TRANSMITTAL OF APPEAL BRIEF

Docket No. 28385/35415US

In re Application of: James W. Williams, et al.

Application No.	Filing Date	Examiner	Group Art Unit
09/529,053	April 6, 2000	S. Wang	1617

Invention: ANTI-VIRAL USES OF LEFLUNOMIDE PRODUCTS

TO THE COMMISSIONER OF PATENTS:

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Dated: June 22, 2004 Signature: (Richard Zimmermann)

PATENT
ATTORNEY DOCKET 28385/35415

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	)	For: Anti-Viral Uses of Leflunomide Products
Williams *et al.*	)	Group Art Unit: 1617
Serial No: 09/529,053	)	
Filed: April 6, 2000	)	Examiner: S. Wang

APPELLANTS' BRIEF UNDER 37 C.F.R. §1.192

1. REAL PARTY IN INTEREST

Appellants are James Williams, M.D. and the Ohio State University Research Foundation, by virtue of an assignment from W. James Waldman, Ph.D. Appellants are the real parties in interest, as recorded at Reel 10799, Frame No. 0010.

2. RELATED APPEALS AND INTERFERENCES

There are no pending appeals or interferences related to the present Application.

3. STATUS OF CLAIMS

Claims 1-15 were previously cancelled from the Application. Claims 16-25 are pending in the form set out in Appendix A, attached hereto, and stand finally rejected under 35 U.S.C. §103, as set out in the Office Action mailed March 23, 2004. All rejections to claims 16-25 are being appealed.

4. STATUS OF AMENDMENTS

No amendment was filed after the Final Office Action of March 23, 2004.

5. SUMMARY OF THE INVENTION

One of the consistent side effects of the use of immunomodulatory compounds such as cyclosporine to inhibit rejection of organ transplants is an increased incidence of viral and bacterial infection. Appellants discovered that immunomodulatory leflunomide products, e.g. leflunomide (HWA486), N-(4-trifluoromethylphenyl)-5-methylisozole-4-carboxamide (Figure I) and its principle metabolite, (A771726) N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide (Figure 2) inhibit viral virion assembly in virus-infected cells.

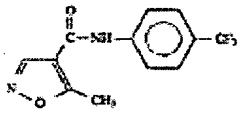

FIGURE I

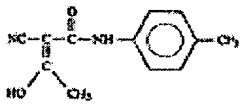

FIGURE 2

The specification of the Application presents multiple working examples of both *in vivo* and *in vitro* anti-viral effects of leflunomide products including, in example 10, a case study of a liver transplant patient maintained on cyclosporine who was encountering chronic hepatitis C infection. "Swapping" leflunomide for cyclosporine, the patient experienced a 50% drop in viral load after six weeks of treatment.

Leflunomide products interfere with the assembly of viral virion components in the cell cytoplasm, in contrast to other known anti-viral products, which generally interfere with replication of viral DNA. This inhibition is shown particularly in Example 5 (contrasting the appearance of complete virions measuring just over 200 nM in untreated, cytomegalovirus (CMV)-infected cells, with the apparent failure of viral particle formation beyond the 100 nM naked capsid stage in CMV-infected cells treated with the metabolite of leflunomide); and Example 8c (similar contrasts between Herpes Simplex Virus (HSV)-infected cells untreated and treated with the metabolite).

To date, the leflunomide products described by Appellants are the only known therapeutic compounds that in and of themselves provide both anti-inflammatory effects and anti-viral effects in humans. Sole independent claim 16 is directed to:

> 16. A method for inhibiting viral replication in cells susceptible to viral infection comprising contacting said cells with a leflunomide product in an amount effective to inhibit viral virion assembly.

6. ISSUES PRESENTED

Has the Examiner established *prima facie* obviousness of the subject matter of claims 16-25 based on the teachings of two "primary" references, either standing alone, or in various combinations with three "secondary" references and, if so, has that *prima facie* case for obviousness been rebutted by objective evidence presented by way of expert declarations?

7. GROUPING OF CLAIMS

A. Claims 16, 17, 20, 21, 24 and 25 stand rejected as assertedly obvious on the basis of Weithmann *et al.*, U.S. Patent No. 5,556,870 (hereafter "Weithmann"), and separately on the basis of Coghlan *et al.*, WO 94/24095 (hereafter "Coghlan"), in view of McChesney *et al.*, *Transplantation*, 57:1717-1722 (1994) (hereafter "McChesney").

B. Claim 18, directed to use of the primary metabolite of leflunomide, stands rejected as assertedly obvious on the basis of Coghlan in view of McChesney.

C. Claim 19, directed to inhibiting herpesvirus, stands rejected as assertedly obvious on the basis of Weithmann in view of Flamand *et al.*, *J. Virol*, 65:5105-5110 (1991) (cited as CAPLUS Abstract, AN 1991:581163 (hereafter "Flamand") and separately on the basis of Coghlan in view of McChesney.

D. Claim 22, directed to the use of another anti-viral agent, and claim 23, directed to the use of a pyrimidine, stand rejected as assertedly obvious on the basis of Weithmann in view of Hammer, *AIDS*, 10: supp. 3, s1-s11 (1996) (hereafter "Hammer") and separately on the basis of Coghlan, in view of McChesney, in further view of Hammer.

The "peppering" of the claims with separate alternative final rejections based on the two primary references alone or in multiple combinations with the secondary references has the following effect. If the rejection of the claims based on Coghlin is reversed, only claim 18 will be allowable, unless the rejections of the remaining claims based on the disclosures of Weithmann are also reversed.

8. ARGUMENT

A. The Appellants submit that no *prima facie* case has been made by the Examiner for obviousness of the subject matter of claims 16-25 based on the teachings of the two "primary" references either standing alone, or in combination with any of the three "secondary" references. Even if the Examiner had established such *prima facie* obviousness, it has been successfully rebutted by objective evidence presented by way of expert declarations. The outstanding rejections under 35 U.S.C. §103 should therefore be reversed.

i. Brief summary of the cited art

There are two primary and three secondary references cited:

Primary:

Weithmann proposes therapeutic use of leflunomide (HWA486) to inhibit interleukin 1 beta (IL-1β) synthesis by variously-diseased humans or animals suffering from leukemia, hepatitis, increased cartilage absorption, HIV infection, Alzheimer's disease, muscle breakdown, meningitis, microbacterial infections, thromboses, arteriosclerotic depositions, elevated fat level and joint destruction (Claim 1). Weithmann "exemplifies" such uses with the *in vitro* showing of reduction of IL-1β secretion by blood cells stimulated with bacterial endotoxin (*Salmonella* lipopolysaccharide, Col. 3, lines 54-56) under conditions designed to prevent formation of the assertedly "non-inhibitory" leflunomide metabolite, A771726 (Col. 1, lines 50-54).

Coghlan addresses preparation of immunosuppressant isoxazole compounds that would have a lesser half-life than leflunomide and its primary metabolite and assertedly avoid "the serious side effects frequently associated with immunosuppressant therapy such as increased risk of malignancy or prolonged susceptibility to viral or other infections." (Page 2, lines 24-26). Pages 3 and 4 of Coughlin provide an exhaustive list of over a hundred disparate disease states, including hepatitis, which assertedly may be either prevented or treated through use of the new immunosuppressant isoxazole compounds.

Secondary:

McChesney addresses the immunosuppressive effects of leflunomide alone and in combination with cyclosporine in dogs that have undergone kidney allograft transplantation, noting that none of the dogs developed bacterial or viral infections (Abstract).

Flamand addresses IL-1β production by virally-infected cells.

Hammer addresses and provides structures of anti-retroviral agents including various nucleoside analog reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, acyclic nucleoside phosphatase reverse transcriptase inhibitors and protease inhibitors.

ii. The outstanding final rejections

Claims 16, 17, 20, 21, 24 and 25 were finally rejected under 35 U.S.C. §103(a) as assertedly rendered obvious by Weithmann for the reasons set out in the Action dated September 19, 2003. Briefly reiterated, it was the Examiner's position that:

> Weithmann et al. teach a method of treating disorder [sic] in which interleukin 1 beta is involved. The disorders include viral infections, such as HIV or hepatitis, comprising administering leflunomide to the patient.

Claim 19 was finally rejected under 35 U.S.C. §103(a) as assertedly rendered obvious by Weithmann, in view of Flamand, for the reasons set out in the Action dated September 19, 2003. Briefly reiterated, it was the Examiner's position that:

> Flamand et al. teaches that herpes infection is involved with interleukin 1 beta. See, particularly, the abstract.

Claims 22 and 23 were finally rejected under 35 U.S.C. §103(a) as assertedly rendered obvious by Weithmann, in view of Hammer, for the reasons set out in the Action dated September 19, 2003. It was the Examiner's position that:

> [H]ammer teaches that several pyrimidin [sic] compounds are known antiviral agents. See, particularly, page s3.

Claims 16-20, 24 and 25 were finally rejected under 35 U.S.C. §103(a) as assertedly rendered obvious by Coghlan in view of McChesney, for the reasons set out in the Action dated September 19, 2003. It was the Examiner's position that:

> Coghlan et al. teaches compounds with general structures that encompass leflunomide or its active metabolite, the compounds have similar biological activity of leflunomide or its metabolite. See, particularly, the abstract, page 2, the examples and the claims. The expressly taught compounds include those meet the leflunomide products (page 18-19 in the specification). Homologue of leflunomide (e.g. 5-mthyl-isoazole-4-carboxylic acid 2,2,2, trifloroethyl-amide) have been expressly disclosed (page 10, line 35). These compounds are known to be useful for treating or preventing viral infection such as hepatitis and cytomegalovirus infection, particularly, HCMV. See, page 4, lines 23-32.
>
> McChesney teaches that both leflunomide and A771726 are known to be effective in preventing viral infection. See, particularly, the abstract at page 1717, and the materials and method at page 1717-1718.

Claims 22 and 23 were finally rejected under 35 U.S.C. §103(a) as assertedly rendered obvious by Coghlan in view of McChesney, in further view of Hammer, for the reasons set out in the Action dated September 19, 2003. It was the Examiner's position that:

> [H]ammer teaches that several pyrimidin [sic] compounds are known antiviral agents. See, particularly, page s3.

B. No *prima facie* case has been made by the Examiner for obviousness of the subject matter of claims 16-25

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness; only if that burden is met, does the burden of coming forward with evidence or argument shift to applicant. *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993), citing *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). A *prima facie* case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *Id.*, citing, *In re Bell*, 991 F.2d 781, 782 (Fed. Cir. 1993), quoting, *In re Rinehart*, 531 F.2d 1048, 1051 (CCPA 1976).

i. There is no *prima facie* obviousness of claims 16-17, 19-25 based on Weithmann

Appellants submit that no *prima facie* case of obviousness of the claimed subject matter can properly be supported by the teachings of the Weithmann reference. It is the Examiner's position that:

> Weithmann et al. teach a method of treating disorder in which interleukin 1 beta is involved. The disorders include viral infections, such as HIV or hepatitis, comprising administering leflunomide to the patient. See particularly the abstract and the claim. (Office Action of September 23, 2003)

Weithmann at best asserts only that *in vitro* tests of un-metabolized leflunomide (HWA 486) suggest activity in modulating the secretion of IL-1β by cells from patients having any number of diseases, including viral infections. Weithmann states that leflunomide (HWA 486) is rapidly metabolized upon administration to form an active metabolite (A771726) (column 1, lines 9-37), but then observes that leflunomide, but not its metabolite, has activity in inhibiting cytokine "synthesis and liberation" (*See* Column 1, lines 45-49). Weithmann then demonstrates *in vitro* an IL-1β reduction effect in a specially-prepared isolated blood cell fraction which was designed not to metabolize leflunomide to any appreciable extent (*See* particularly column 3, lines 23-26 and Example 1), but never addressed how to provide the special *in vitro* test conditions *in vivo*, i.e., how to prevent

leflunomide from being metabolized promptly upon administration as Weithmann admits will rapidly occur.

The sole claim of Weithmann (reproduced below) is not directed to a method of treating viral infections but rather a method for treating elevated levels of interleukin 1 beta by administering leflunomide to patients suffering from a wide variety of diseases for the purpose of and in an amount sufficient to inhibit the synthesis and liberation of said interleukin:

> 1. A method for the treatment of a condition characterized by an elevated interleukin 1 beta level in a human or animal suffering from leukemia, hepatitis, increased cartilage absorption, HIV infection, Alzheimer's disease, muscle breakdown, meningitis, microbacterial infections, thromboses, arteriosclerotic depositions, or elevated fat level and joint destruction, wherein the method comprises administering to said human or animal N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide in an amount sufficient to inhibit the synthesis and liberation of said interleukin.

Weithmann's experimental is directed to leflunomide's effect on avoiding the adverse activity of IL-1β, not leflunomide's effect on the treatment of underlying disease states and disorders. There is no data in Weithmann to suggest otherwise.

In contrast, Appellants show *in vitro* and *in vivo* examples of leflunomide products, which include the metabolite, effectively inhibiting viral replication. Further, Appellants' claims require that leflunomide products inhibit viral virion assembly. The Examiner's position is that this limitation, "does not carry patentable weight since it does not distinct [sic] the method herein from the method suggested by prior art." (Office Action of March 23, 2004) This is incorrect. The mode of action suggested in Weithmann -- use of leflunomide to suppress IL-1β proliferation -- provides no disclosure or suggestion that leflunomide would inhibit viral virion assembly.

Further, for claim 24 to be *prima facie* obvious, one reasonably skilled in the art would have to know leflunomide inhibited viral virion assembly because claim 24 is directed to the use of leflunomide products to inhibit replication of viruses that are resistant to drugs that inhibit viral DNA replication. There was no such knowledge in the art, let alone in Weithmann. The Examiner has made no suggestion otherwise.

For these reasons, Appellants believe the Examiner has failed to establish that any *prima facie* case of obviousness of the claimed subject matter can properly be made out through application of the Weithmann reference.

Even when obviousness is based on a single prior art reference, there must be a showing or a suggestion or motivation to modify the teachings of the reference. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). Nowhere in the entirety of the record does the Examiner show any suggestion or motivation, either from Weithmann or the knowledge generally available in the art that leflunomide would act as an anti-viral agent and inhibit viral virion assembly as claimed. The Examiner has not met the burden of presenting a *prima facie* case of unpatentability.

ii. There is no *prima facie* obviousness of claim 19 based on Weithmann in view of Flamand

Claim 19 is directed to a method of inhibiting the virion assembly of herpesvirus with a leflunomide product. No *prima facie* case of obviousness can be made out through combination of Weithmann with the disclosure of the secondary reference, Flamand, because Flamand does not supply a teaching of the claimed elements to remedy the lack of such teaching in Weithmann.

It is the Examiner's position that, "Flamand et al. teaches that herpes infection is involved with interleukin 1 beta. See, particularly, the abstract." Flamand discusses that human herpesvirus 6 (HHV-6) induces IL-1β and tumor necrosis factor alpha (but not interleukin 6 synthesis) in peripheral blood mononuclear cells. HHV-6's suggested capacity to stimulate cells of myeloid lineage to produce IL-1β suggests nothing regarding the treatment of HHV-6. There is no suggestion or motivation that any therapeutic agent capable of inhibiting the production of IL-1β would also be capable of inhibiting virus replication in the infected patient.

The mere "involvement" between herpesvirus and IL-1β does not suggest that leflunomide is effective in treating herpesvirus. The Flamand disclosure does not supplement the disclosure deficiencies of Weithmann. In neither reference is there any suggestion that inhibiting IL-1β would inhibit viral replication, much less herpesvirus replication *in vivo*. Flamand says nothing about anti-viral inhibitors, certainly nothing about leflunomide products inhibiting anything, let alone viral virion assembly (as claimed by Appellants). The Examiner has not established a *prima facie* case of obviousness of claim 19 on the basis of Weithmann in view of Flamand.

iii. There is no *prima facie* obviousness of claims 22 and 23 based on Weithmann in view of Hammer

It further follows that no *prima facie* case of obviousness can be made out through combination of Weithmann with the disclosure of secondary reference Hammer. Weithmann does not teach that leflunomide products were known anti-viral agents. Hammer is a review article, "... of studies detailing the efficacy of the anti-retroviral agents and combinations furthest along in clinical development and the application of plasma HIV RNA quantification as a disease marker." (*See* Abstract) The Examiner points to Hammer's discussion of combination therapy for its applicability as a secondary reference and to support the belief that one of ordinary skill in the art to combine it with Weithmann to render obvious the subject matter of claims 22 and 23:

> The argument that combination therapy would ultimately be the best approach to the management of HIV disease has been put forth ever since agents beyond ZDV became available, and although supported by a number of phase II trials demonstrating greater marker responses with combination therapy, it is only recently that the clinical superiority of this approach over ADV monotherapy has been proven. (Hammer, Page 52)

As a preliminary matter, claims 22 and 23 are not directed to the same subject matter. Claim 22 is directed to the co-administration of leflunomide products and another anti-viral agent. Claim 23 is directed to co-administration of leflunomide products with a pyrimidine. Leflunomide products inhibit dihydroorotate dehydrogenase, a key enzyme in the biosynthesis of pyrimidines. Appellants disclose and claim the co-administration of leflunomide products with a pyrimidine, "in order to reduce its [the leflunomide products'] potential toxicity while maintaining its therapeutic effectiveness." (Pages 20-21 of the Application)

Neither Weithmann nor Hammer have <u>any</u> discussion of co-administering a pyrimidine with leflunomide (or with any anti-viral agent) to <u>stimulate</u> DNA synthesis. Rather, the various nucleoside analogue reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, acyclic nucleoside phosphate reverse transcriptase inhibitors and protease inhibitors of Hammer are taught to <u>prevent</u>, as opposed to <u>facilitate</u>, DNA synthesis. Since Hammer teaches the opposite effect of that stated by the Appellants, one of ordinary skill in the art would not have combined Hammer with Weithmann.

Further, one of ordinary skill in the art would not have been motivated to combine Hammer's suggestion that co-administration of certain anti-viral agents are beneficial when treating HIV to prevent DNA synthesis with Weithmann. Weithmann does not address novel antiviral agents. Hammer's disclosure does not supply the missing elements from Weithmann's disclosure. The Examiner has not established a *prima facie* case of obviousness of claims 22 or 23 on the basis of Weithmann in view of Hammer.

iv. There is no *prima facie* obviousness of claims 16-25 based on Coghlan and in view of McChesney

None of the claims stand rejected on the basis of Coghlan alone. One of ordinary skill in the art would not have been motivated to combine the disclosure of the Coghlan reference with that of the McChesney reference, or have found the individual teachings therein sufficient to support a *prima facie* case of obviousness for the Appellants' claimed subject matter.

Coghlan addresses the synthesis of compounds "having immunomodulatory activity" (page 1, line 6-7) and lists disease states assertedly treatable with such immunomodulatory agents (page 3, line 1 - page 4, line 30). This list includes virtually every conceivable illness having a direct or indirect immunological component and concludes with reference to a few viral diseases. The sole assay for biological activity (Example 295) is a mixed lymphocyte test, having no connection whatsoever to the assessment of anti-viral activity, nor is it suggested to show such activity. Not one single scientific publication is cited for a showing of efficacy of these isoxazole compounds in any of the disease states listed. Further, Coghlan is not a "scientific publication" as asserted by the Examiner, but rather a non-peer reviewed published patent application, that has not issued as a patent, and does not teach that isoxazole compounds structurally related to leflunomide products inhibit viral replication as claimed by Appellants.

Even if Coghlan taught isoxazole compounds suitable for treating all these disparate disease states, such as hepatitis, the compounds attributed to providing this treatment are not leflunomide products. Rather, these isoxazole compounds are contrasted as having lesser half-lives than leflunomide products. One of ordinary skill in the art would not select leflunomide products based upon the contrasted description of the properties of the isoxazole compounds purported to have an immunological component. The Examiner refers to *In re Lambert and Konor* (all disclosures of prior art, including unpreferred embodiments, must be considered). These cases do not suggest or imply that different half-lives are an unpreferred characteristic. Different half-lives of the new isoxazole compounds lead one of ordinary skill in the art away from compounds with half-lives like leflunomide products. Further, no subject matter is rejected on the basis of Coghlan alone, but rather in view of McChesney. McChesney does not correct the deficiencies in the teaching of Coghlan.

One of ordinary skill in the art would not be motivated to combine Coghlan with McChesney. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of

persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.) In order to be so motivated, one of ordinary skill in the art would need to see a suggestion that McChesney addressed the use of leflunomide as an anti-viral agent.

McChesney shows immunosuppressive effects of leflunomide alone and with cyclosporine in canines with kidney allograft transplants. The only mention in McChesney of viral infection is a statement in the abstract that, "Even at a high dose of 16mg/kg/day no viral or bacterial infections were noted." The McChesney reference includes no experimental procedures for assessing antiviral or antibacterial effects of leflunomide.

Clearly then, the combined Coghlan and McChesney references provide no suggestion whatsoever in their disclosures to those of ordinary skill in the art that leflunomide products had been found to be effective in inhibiting viral virion assembly or might be tested for such effects with any reasonable expectation of success. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *In re Fritch*, 972 F.2d (Fed. Cir. 1992), citing *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991). The Examiner has not met his burden of establishing a *prima facie* case of obviousness with Coghlan in view of McChesney.

v. There is no *prima facie* obviousness of claims 22 and 23 based on Coghlan, in view of McChesney, in further view of Hammer

It further follows that no *prima facie* case of obviousness can be made out through combination of Coghlan and McChesney with the disclosure of secondary reference Hammer. As discussed above, Hammer discloses that combination therapy was recently discovered to be clinically superior over monotherapy in treating HIV. Claim 22 is directed to co-administration of leflunomide products and another anti-viral agent. The disclosures of Coghlan and McChesney do not teach that leflunomide products are anti-viral agents and thus one of ordinary skill in the art would not have been motivated to combine the teachings in these references with the disclosure in Hammer.

Claim 23 is directed to co-administration of leflunomide products with a pyrimidine. Coghlan, McChesney and Hammer have no discussion of co-administering a pyrimidine with leflunomide, or with any other anti-viral agent, to reduce potential toxicity of the anti-viral drug while maintaining its therapeutic effectiveness. In fact, Hammer provides structures of anti-retroviral agents including various nucleoside analog reverse transcriptase inhibitors,

non-nucleoside reverse transcriptase inhibitors, acyclic nucleoside phosphatase reverse transcriptase inhibitors and protease inhibitors to prevent, rather than facilitate, DNA synthesis. The Examiner has not explained how Hammer supplies a teaching of the deficiencies in Coghlan and McChesney to derive the claimed invention. Therefore, has not met the burden of establishing a *prima facie* case of obviousness.

C. Even if the Examiner had established such *prima facie* obviousness, it has been successfully rebutted by objective evidence.

i. Rebuttal of assertion that Weithmann renders *prima facie* obviousness subject matter of claims 16-25

The Appellants submitted the Declaration of W. James Waldman, Ph.D. to address Weithmann. According to Dr. Waldman:

> Weithmann actually contains no disclosure or suggestion that any leflunomide product possesses anti-viral activity. Further, the *in vitro* experimental results set out in Weithmann do not constitute any creditable scientific basis whatsoever for the proposed therapeutic utility (i.e., reduced elevated interleukin 1 beta levels) in animals, including humans. (Waldman Declaration, para. 4)

According to the Declaration of Dr. Waldman, "Most significantly, Weithmann never proposes that leflunomide has any direct action or effect on virus replication. Contrary to the position taken by the Examiner, treatment with leflunomide is not established by Weithmann as 'a method known to be useful for treating viral infection.'" (Waldman Declaration, para. 4) The Examiner's only comments of record regarding Dr. Waldman's Declaration are as follows:

> The declaration under 37 CFR 1.132 filed June 26, 2003 is insufficient to overcome the rejection of claims 16, 17, 19-25 based upon Weithmann *et al.* as set forth in the last office action because: applicants' attack of Weithmann reference is not probative. Particularly, Weithmann specifically claimed method of treating HIV infection hepatitis [sic] with one of leflunomide products. Further, since every patent is presumed valid, and since that presumption includes the presumption of operability, examiners should not express any opinion on the operability of a patent. Affidavits or declarations attacking the operability of a patent cited as a reference must rebut the presumption by a preponderance of the evidence. (Office Action mailed 9/23/03, para. 14, citations omitted).

Appellants are not disputing the validity of Weithmann for what it teaches. Appellants are disputing the Examiner's interpretation of the teaching. According to the Declaration of Dr. Waldman, an accurate scientific assessment of Weithmann would not

suggest to one of ordinary skill in the art that leflunomide would have anti-viral effects. Taking Weithmann at face value, if leflunomide was capable of modulating IL-1β secretion, leflunomide would be an immunosuppressive/ anti-inflammatory agent. As discussed in the Waldman Declaration and the references appended thereto, it would have been counter-intuitive for one skilled in the art to expect an immunosuppressive/anti-inflammatory agent to perform as an anti-viral agent, as it is well documented that agents with anti-inflammatory properties (such as modulating IL-1β secretion) enhance prospects for developing viral disease.

Further, the Waldman Declaration provided experimental evidence of more recent *in vitro* studies confirming Appellants' assertion that leflunomide's bi-functionality is not shared by other immunosuppressive agents (See Waldman Declaration, para. 7), as well as *in vivo* studies in press at the time of the Declaration. (Id., para. 8).

> I am aware of no data in the literature (whether in vivo or in vitro) or in practice clinically that correlates immunosuppressive effect to useful anti-viral activity, with the exception of in vitro reports on mycophenolic acid or mycophenolate mofetil (MMF) (Roche Pharmaceuticals) inducing apoptosis of activated CD4+T lymphocytes (major host cell for HIV) and inhibiting HIV isolation from CD4+T cell populations. Chapius et al. Nat Med 2000; 6:762-768, (2000). (Id. para. 9).

Dr. Waldman goes on to distinguish MMF by the fact that it exerts no detectable anti-viral activity by itself, has not had efficacy in clinical studies, and is structurally distinct from leflunomide. Finally, Dr. Waldman dispelled through experimental data the possibility that leflunomide's activity as a tyrosine kinase inhibitor would suggest a potential anti-viral connection. Thus, even six years after the filing of Appellants' invention, one of ordinary skill in the art would not find it obvious from Weithmann that leflunomide would have any anti-viral effect. The entirety of the Examiner's remarks in the Final Action on Weithmann are:

> With respect to the declaration by Edward s. Mocarski [sic] under 37 CFR 1.132 filed June 26, 2003, note the examiner did not simply ignore the declaration. The evidence of nonobviousness provided in the declaration is not sufficient to outweigh the obviousness evidence provided by the prior art. Applicants' opinion and comments about Weithmann's mechanistic interpretation can not negate the fact that Weithmann teaches to use leflunomide for treating viral infection (see the claim). As discussed in prior office action, the functional limitation "for inhibiting viral replication in cells," does not carry patentable weight since it does not distinct [sic] the method herein claimed from the method suggested by prior art. (Office Action of March 23, 2004.)

The Mocarski Declaration does not address Weithmann. Weithmann suggests no method of viral treatment. The Examiner has provided no evidence to Appellants' rebuttal that Weithmann discloses or assuredly rendered obvious Appellants' claimed elements directed to inhibition of viral activity, certainly not inhibition of viral virion assembly. Further, for claim 24 to be *prima facie* obvious, one reasonably skilled in the art would have to know leflunomide inhibited viral virion assembly because claim 24 is directed to the use of leflunomide products to inhibit replication of viruses that are resistant to drugs that inhibit viral DNA replication. There was no such knowledge in the art, let alone in Weithmann. The Examiner has made no suggestion otherwise.

Even if the Examiner has established a *prima facie* case that the subject matter of claims 16-25 are obvious in view of Weithmann, Appellants have successfully rebutted such case. The secondary references similarly fall.

ii. Rebuttal of the assertion that Coghlan in view of McChesney renders *prima facie* obviousness the subject matter of claims 16-25

Coghlan discloses isoxazole compounds: (a) structurally distinct from leflunomide products; (b) that are contrasted for having a lesser half-life than leflunomide products; and (c) are purported to treat over one hundred disease states. That said, no claim is rejected on the basis of Coghlan alone, rather only in view of McChesney alone or in further view of Hammer.

As confirmed in the Declaration of Edward S. Mocarski, the Examiner's position is simply not supported by the disclosures of McChesney reference. The Examiner has provided no explanation as to why the Mocarski Declaration is not dispositive.

McChesney evaluates the immunosuppressive effects of leflunomide alone and in combination with cyclosporine in dogs undergoing kidney allograft transplantation. The only mention in McChesney of viral infection is a statement in the abstract that, "Even at a high dose of 16mg/kg/day no viral or bacterial infections were noted." The McChesney reference includes no experimental procedures for assessing antiviral or antibacterial effects of leflunomide. There is nothing reported in the reference to support or explain this statement, which would be necessary in order to attribute the cause for such an observation to the administered drugs (See Mocarski Declaration, specifically para. 5). Moreover, it is not surprising that McChesney noted this lack of viral infection. Institutional animal care guidelines (followed by McChesney according to page 1721) require full vaccination of animals. (Id.)

Even if the Examiner has established a *prima facie* case that the subject matter of claims 16-25 are obvious in light of Coghlan in view of McChesney and Hammer, Appellants have successfully rebutted such case with objective evidence and the declaration of Dr. Mocarski. The secondary references similarly fall.

D. Conclusion

Based on the foregoing, Appellants submit that no *prima facie* case has been made by the Examiner for obviousness of the subject matter of claims 16-25 based on the teachings of the two "primary" references either standing alone, or in combination with the three "secondary" references. Even if the Examiner had established such *prima facie* obviousness, it has been successfully rebutted by objective evidence presented by way of expert declarations of Drs. Waldman and Mocarski. The outstanding rejections of Claims 16-25 under 35 U.S.C. §103 should therefore be reversed.

Respectfully submitted,

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APPENDIX A

LISTING OF CLAIMS

Claims 1-15 (previously canceled)

Claim 16 (previously presented). A method for inhibiting viral replication in cells susceptible to viral infection comprising contacting said cells with a leflunomide product in an amount effective to inhibit viral virion assembly.

Claim 17 (previously presented). The method of claim 16 wherein the leflunomide product is N-(4-trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide (HWA 486).

Claim 18 (previously presented). The method of claim 16 wherein the leflunomide product is N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamde (A771726).

Claim 19 (previously presented). The method of claim 16 wherein the virus is a herpesvirus.

Claim 20 (previously presented). The method of claim 16 wherein the virus is selected from the group consisting of paramyxoviruses, pricornaviruses and hepatitis viruses.

Claim 21 (previously presented). The method of claim 16 wherein the virus is selected form the group consisting of CMV, HSV, measles virus, rhinoviruses, hepatitis B and hepatitis C.

Claim 22 (previously presented). The method of claim 16 further comprising contacting the cells with another anti-viral agent.

Claim 23 (previously presented). The method of claim 16 further comprising contacting the cells with a pyrimidine.

Claim 24 (previously presented). The method of claim 16 wherein the virus is resistant to anti-viral agents that inhibit viral DNA replication.

Claim 25 (previously presented). The method of claim 16 wherein cells are virally infected.--